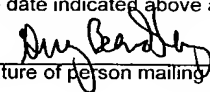


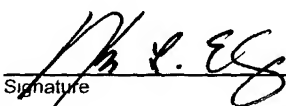

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Guy Beardsley Printed name of person mailing correspondence		 Signature of person mailing correspondence

Substitute Form PTO 1390 U.S. Department of Commerce Patent and Trademark Office TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		Attorney's Docket Number: 00786/376002 U.S. Application Number: Not yet assigned
INTERNATIONAL APPLICATION NUMBER PCT/US00/26634		INTERNATIONAL FILING DATE September 28, 2000
		PRIORITY DATE CLAIMED September 30, 1999
TITLE OF INVENTION: APPLICANTS FOR DO/EO/US:		USE OF PRAMIPEXOLE AS A TREATMENT FOR COCAINE CRAVING JERROLD ROSENBAUM
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1.	<input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. § 371	
2.	<input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. § 371	
3.	<input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. § 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. § 371(b) and PCT Articles 22 and 39(1).	
4.	<input type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19 th month from the earliest claimed priority date	
5.	A copy of the International Application as filed (35 U.S.C. § 371(c)(2)). <input checked="" type="checkbox"/> a. is transmitted herewith (required only if not transmitted by the International Bureau). <input type="checkbox"/> b. has been transmitted by the International Bureau. <input type="checkbox"/> c. is not required, as the application was filed with the United States Receiving Office (RO/US).	
6.	<input type="checkbox"/> A translation of the International Application into English (35 U.S.C. § 371(c)(2)).	
7.	Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. § 371(c)(3)). <input type="checkbox"/> a. are transmitted herewith (required only if not transmitted by the International Bureau). <input type="checkbox"/> b. have been transmitted by the International Bureau. <input type="checkbox"/> c. have not been made; however, the time limit for making such amendments has NOT expired. <input checked="" type="checkbox"/> d. have not been made and will not be made.	
8.	<input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. § 371(c)(3)).	
9.	<input checked="" type="checkbox"/> An oath or declaration of the inventors (35 U.S.C. § 371(c)(4)) (unsigned).	
10.	<input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. § 371(c)(5)).	
11.	<input type="checkbox"/> An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98.	
12.	<input type="checkbox"/> An assignment for recording. A separate cover sheet in compliance with 37 §§ 3.28 and 3.31 is included.	
13.	<input type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.	
14.	<input type="checkbox"/> A substitute specification.	
15.	<input type="checkbox"/> A change of power of attorney and/or address letter.	
16.	<input type="checkbox"/> Other items or information:	

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17.	<input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 C.F.R. § 1.492(A)(1)-(5)): Neither international preliminary examination fee (37 C.F.R. § 1.482) nor international search fee (37 C.F.R. § 1.455(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$ 1040.00 International preliminary examination fee (37 C.F.R. § 1.482) not paid to USPTO but international search Report prepared by the EPO or JPO \$ 890.00 International preliminary examination fee (37 C.F.R. § 1.482) not paid to USPTO but international search fee (37 C.F.R. § 1.445(a)(2)) paid to USPTO \$ 740.00 International preliminary examination fee (37 C.F.R. § 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1) - (4) \$ 710.00 International preliminary examination fee paid to USPTO (37 C.F.R. § 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$ 100.00				
ENTER APPROPRIATE BASIC FEE AMOUNT =			\$	710.00	
Surcharge of \$130 for furnishing the oath or declaration later than <input type="checkbox"/> 20 OR <input type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(e)).			\$		
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	9 - 20 =	0	x \$18	\$	
Independent claims	2 - 3 =	0	x \$84	\$	
Multiple dependent claims (if applicable)			+ \$280	\$	280.00
TOTAL OF ABOVE CALCULATIONS =			\$	990.00	
Reduction of ½ for filing by small entity, if applicable Applicant claims small entity status under 37 C.F.R. § 1.27.			\$	495.00	
SUBTOTAL =			\$	495.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 OR <input type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(f))			+	\$	
TOTAL NATIONAL FEE =			\$	495.00	
Fee for recording the enclosed assignment (37 C.F.R. 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§ 3.28, 3.31). \$40.00 per property.			+	\$	
TOTAL FEES ENCLOSED =			\$	495.00	
			Amount to be refunded	\$	
			charged	\$	
<input checked="" type="checkbox"/> a. A check in the amount of \$495.00 to cover the above fees is enclosed. <input type="checkbox"/> b. Please charge my Deposit Account No. 03-2095 in the amount of \$ [***] to cover the above fees. <input checked="" type="checkbox"/> c. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 03-2095.					
NOTE: Where an appropriate time limit under 37 C.F.R. §§ 1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. § 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: Karen L. Elbing, Ph.D. Clark & Elbing LLP 101 Federal Street Boston, MA 02110 Telephone: 617-428-0200 Facsimile: 617-428-7045 Customer No.: 21559			Signature  Karen L. Elbing, Ph.D. Reg No. 35,238 		

21559

PATENT TRADEMARK OFFICE

1/17

USE OF PRAMIPEXOLE AS A TREATMENT FOR COCAINE
CRAVING

5

Background of the Invention

This invention relates to methods for the treatment of cocaine craving.

Cocaine is a highly addictive psychostimulant that causes sensations of euphoria and craving, resulting in physiological as well as psychological damage. Although cocaine use leads to a multitude of physiological complications, its primary target of action is the central nervous system. Cocaine withdrawal following abstinence causes, among other symptoms, an intense craving for the abused drug, which in turn frequently results in the relapse into renewed drug use. Epidemiological studies point to a high incidence of multiple substance abuse among cocaine users, a finding that has significant societal and medical repercussions.

To date, approved pharmacotherapies for cocaine abuse and dependence have proven scarce despite the acute need for such therapies.

20

Summary of the Invention

In general, the invention features methods for treating stimulant dependencies, such as cocaine craving, by administering a therapeutically-effective amount of a dopamine agonist, for example, pramipexole.

In one aspect, the invention provides a method of treating a patient (for example, a human) with a stimulant dependency by administering a

25

therapeutically-effective amount of pramipexole to the patient. In preferred embodiments of this aspect, the stimulant dependency is a stimulant craving and the stimulant is cocaine.

In a related aspect, the invention provides a method of treating a human diagnosed with cocaine craving by administering a therapeutically-effective amount of pramipexole to the human.

In preferred embodiments of both of the above aspects of the invention, the method further includes administering a therapeutically-effective amount of an antidepressant or an anticonvulsant, for example, lamotrigine.

By "treating" is meant the medical management of a patient with the intent that a cure, amelioration, or prevention of a dependency or a relapse or associated disease, pathological condition, or disorder will result. This term includes active treatment, that is, treatment directed specifically toward improvement of the dependency or associated cure of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the dependency or associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the dependency, disease, pathological condition, or disorder; preventive treatment, that is, treatment directed to prevention of the dependency or associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the dependency or associated disease, pathological condition, or disorder. The term "treating" also includes symptomatic treatment, that is, treatment directed toward constitutional symptoms of the dependency or an associated disease, pathological condition, or disorder.

By "stimulant" is meant any substance that temporarily increases functional activity, and preferably cardiac, respiratory, cerebral, nervous, vascular, motor, or vasomotor functional activity. Preferred stimulants include, without limitation, cocaine, amphetamines, methamphetamine, and
5 methylphenidate.

By "therapeutically-effective amount" is meant an amount of a pramipexole compound sufficient to produce a healing, curative, or ameliorative effect either in the treatment of a stimulant dependency or in the symptoms of a stimulant dependency, for example, cocaine craving.

10 By "dependency" is meant any form of behavior that indicates an altered or reduced ability to make decisions resulting, at least in part, from the use of stimulants. Representative forms of dependency behavior may take the form of antisocial, inappropriate, or illegal behavior and include those behaviors directed at the desire, planning, acquiring, and use of
15 stimulants. This term also includes the psychic craving for a drug that may or may not be accompanied by a physiological dependency, as well as a state in which there is a compulsion to take a drug, either continuously or periodically, in order to experience its psychic effects or to avoid the discomfort of its absence. Forms of "dependency" include habituation, that
20 is, an emotional or psychological dependence on a compound to obtain relief from tension and emotional discomfort, as well as physical or physiological dependence, that is, use of a compound to prevent withdrawal symptoms.

By "craving" is meant a behavior that reflects a consuming desire,
25 longing, or yearning for a stimulant. This term may refer to aspects of behaviors that are components of a dependency.

The present invention provides a number of advantages. Importantly, it provides one of the first therapeutics for the treatment of

stimulant cravings (such as cocaine craving). In addition, the pramipexole utilized herein is non-toxic, is pharmacokinetically understood, and is known to be well tolerated by humans, as is evidenced by its approval for the treatment of Parkinson's Disease.

5 Brief Description of the Drawings

Figure 1 is a schematic illustration of the molecular structure of pramipexole, marketed as Mirapex in the United States.

Detailed Description of the Invention

10 The invention described herein features methods involving the administration of pramipexole (or other dopamine-D3/D2 agonists) for the treatment of stimulant dependency, and preferably for the treatment of cocaine craving and its symptoms, as well as cocaine dependency and associated self-destructive behaviors.

15 Described below is an example of the successful use of pramipexole for the treatment of cocaine craving and related symptoms. This example is provided for the purpose of illustrating the invention, and should not be construed as limiting.

Treatment of Cocaine Craving Using Pramipexole

20 Mr. A, a 34 year-old single, successful business man, was referred for evaluation of possible bipolar disorder. Currently depressed, he had in the previous year brought financial ruin on himself by a pattern of cocaine freebasing and sexual and other extravagance that absorbed nearly one million dollars.

25 Along with current major depression, persisting cocaine craving but rare use, and a question of past primary or secondary (to substance abuse)

mania, he manifested an extraordinary movement disorder with constant restlessness and thrashing of his legs, leaving the inner aspects of his knees and thighs bruised and discolored with hematomas in various stages of evolution and resolution.

5 For the restless legs, he had consulted a neurologist who diagnosed "pre-parkinsonism" presumed secondary to neurological damage from cocaine. The disfiguring movements limited his ability to return to and conduct business.

10 Previously, he had failed to respond to or tolerate most of the new generation of antidepressants. Treatment was begun with lamotrigine up to 200 mg with modest improvement in mood. Given his severe restless legs syndrome and persisting depression, pramipexole was added, titrated to 1.5 mg a day in divided doses.

15 In response to this treatment, his leg movements quieted substantially, his mood brightened, and he reported that these were the first days in a year that he awoke without craving cocaine, a benefit sustained for one year on this drug, combined with 75 mg of lamotrigine. During the subsequent year, Mr. A. reported one day of non-compliance when he was out of town without his medication. That night, for the first time, he dreamt
20 about cocaine and the next day experienced a renewed craving on awakening which resolved when treatment was restored.

 Although he faces an array of financial and business challenges, his mood following treatment is nearly euthymic, his leg movements at worst resemble mild restlessness, and his cocaine craving remains abolished.

25 These dramatic results demonstrate that dopamine agonists, like pramipexole, represent treatments for cocaine craving, and may be particularly useful for patients with comorbid refractory depression.

Pramipexole and Other Dopamine Agonists

The synthesis of pramipexole is described in U.S. Patent No. 4,886,812 and European Patent 186 087. Pramipexole is a non-ergot derivative which may be used at a range of between about 1.5 mg to 6.0 mg
5 per day, and is preferably administered between about 1.5 mg and 4.5 mg per day. Higher dosages may be used with the concomitant risk of potential side effects.

Other formulations for treatment or prevention of stimulant dependency or craving, such as cocaine craving, as described herein, may
10 take the form of a dopamine agonist compound that may be combined with a pharmaceutically-acceptable diluent, carrier, stabilizer, or excipient. Conventional pharmaceutical practice is employed to provide suitable formulations or compositions to administer such compositions to patients. Oral administration is preferred, but any other appropriate route of
15 administration may be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, or aerosol administration. Therapeutic formulations may be in the form of liquid solutions or suspensions (as, for example, for intravenous
20 administration); for oral administration, formulations may be in the form of liquids, tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Methods well known in the art for making formulations are described, for example, in "Remington: The Science and Practice of
25 Pharmacy" (19th ed.) ed. A.R. Gennaro AR., 1995, Mack Publishing Company, Easton, PA. Formulations for parenteral administration may, for

example, contain excipients, sterile water, saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes.

If desired, slow release or extended release delivery systems may be utilized. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

In general, a dopamine agonist for use in the methods of the invention is administered at a dosage appropriate to the effect to be achieved and is typically administered in unit dosage form. As noted above, the preferred route of administration for most indications is oral.

An effective quantity of a dopamine agonist-containing compound of the invention is employed to treat the stimulant dependency or craving, for example, cocaine craving as described herein. The exact dosage of the compound may be dependent, for example, upon the age and weight of the recipient, the route of administration, and the severity and nature of the symptoms to be treated. In general, the dosage selected should be sufficient to prevent, ameliorate, or treat the condition, or one or more symptoms thereof, without producing significant toxic or undesirable side effects.

Combination with Other Therapeutics

One particular source of pramipexole is Pharmacia & Upjohn, Inc. which markets Mirapex (Pramipexole Dihydrochloride) tablets which have the molecular structure shown in Figure 1. Examples of other dopamine
5 agonists include, but are not limited to, amantadine, bromocriptine, cabergoline, lisuride, pergolide, ropinirole, quinpirole, or quinelorane. Pramipexole, or any other dopamine agonist, may be administered as a monotherapy, or in combination with other compounds, for the treatment of multiple substance abuse or other physiological or psychological conditions.

10 In one particular example, the dopamine agonist (e.g. pramipexole) may be administered in combination with an antidepressant, anticonvulsant, antianxiety, antimanic, antipsychotic, antiobsessional, sedative-hypnotic, or stimulant medication. Examples of these medications include, but are not limited to, the antianxiety medications alprazolam, buspirone hydrochloride,
15 chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, desipramine hydrochloride, diazepam, halazepam, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, meprobamate, oxazepam, prazepam, prochlorperazine maleate, prochlorperazine, prochlorperazine edisylate, and trimipramine maleate; the anticonvulsants amobarbital,
20 amobarbital sodium, carbamazepine, chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximide, ethotoin, gabapentin, lamotrigine, magnesium sulfate, mephentoin, mephobarbital, methsuximide, paramethadione, pentobarbital sodium, phenacemide, phenobarbital, phenobarbital sodium, phensuximide,
25 phenytoin, phenytoin sodium, primidone, secobarbital sodium, trimethadione, valproic acid, and clonazepam; the antidepressants amitriptyline hydrochloride, amoxapine, bupropion hydrochloride, clomipramine hydrochloride, desipramine hydrochloride, doxepin

hydrochloride, fluoxetine, fluvoxamine, imipramine hydrochloride,
imipramine pamoate, isocarboxazid, lamotrigine, maprotiline
hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride,
phenelzine sulfate, protriptyline hydrochloride, sertraline hydrochloride,
5 tranylcypromine sulfate, trazodone hydrochloride, trimipramine maleate,
and venlafaxine hydrochloride; the antimanic medications lithium carbonate
and lithium citrate; the antiobsessional medications fluvoxamine, and
clomipramine hydrochloride; the antipsychotic medications acetophenazine
maleate, chlorpromazine hydrochloride, chlorprothixene, chlorprothixene
10 hydrochloride, clozapine, fluphenazine decanoate, fluphenazine enathrate,
fluphenazine hydrochloride, haloperidol decanoate, haloperidol, haloperidol
lactate, lithium carbonate, lithium citrate, loxapine hydrochloride, loxapine
succinate, mesoridazine besylate, molindone hydrochloride, perphenazine,
pimozide, prochlorperazine maleate, prochlorperazine, prochlorperazine
15 edisylate, promazine hydrochloride, risperidone, thioridazine, thioridazine
hydrochloride, thiothixene, thiothixene hydrochloride, and trifluoperzine
hydrochloride; the sedative-hypnotic medications amobarbital, amobarbital
sodium, aprobarbital, butabarbital, chloral hydrate, chlordiazepoxide,
chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam,
20 diphenhydramine, estazolam, ethchlorvynol, flurazepam hydrochloride,
glutethimide, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam,
methotrimeprazine hydrochloride, midazolam hydrochloride, non
prescription, oxazepam, pentobarbital sodium, phenobarbital, phenobarbital
sodium, quazepam, secobarbital sodium, temazepam, triazolam, and
25 zolpidem tartrate; and the stimulants dextroamphetamine sulfate,
methamphetamine hydrochloride, methylphenidate hydrochloride and,
pemoline.

Other Embodiments

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and
5 individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the
10 invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the appended claims.

Other embodiments are within the claims.

15 What is claimed is:

Claims

1. A method of treating a human with a stimulant dependency, said method comprising administering to said human a therapeutically-effective amount of pramipexole.
- 5 2. The method of claim 1, wherein said stimulant dependency involves a stimulant craving.
3. The method of claim 1, wherein said stimulant is cocaine.
4. A method of treating a cocaine craving in a human, said method comprising administering to said human a therapeutically-effective amount
10 of pramipexole.
5. The method of claim 1 or 4, wherein said method further comprises administering to said human a therapeutically-effective amount of an antidepressant.
6. The method of claim 1 or 4, wherein said method further
15 comprises administering to said human a therapeutically-effective amount of an anticonvulsant.
7. The method of claim 6, wherein the anticonvulsant is lamotrigine.

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(71) Applicant (for all designated States except US): THE GENERAL HOSPITAL CORPORATION [US/US]; 55 Fruit Street, Boston, MA 02114 (US).

(81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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— *With international search report.*

(72) Inventor; and

(75) **Inventor/Applicant (for US only): ROSENBAUM, Jerrold [US/US]; 587 Walnut Street, Newton, MA 02460 (US).**

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/22820 A1

(54) Title: USE OF PRAMIPEXOLE AS A TREATMENT FOR COCAINE CRAVING

(57) **Abstract:** Disclosed herein are methods for reducing stimulant dependency or craving, involving administration of a therapeutically-effective amount of a dopamine agonist, such as pramipexole.

1/1

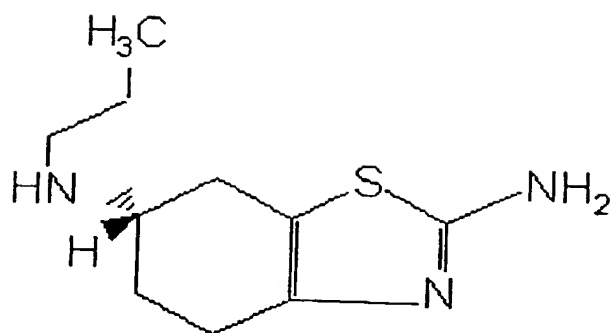


FIGURE 1

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled USE OF PRAMIPEXOLE AS A TREATMENT FOR COCAINE CRAVING, the specification of which

■ was filed on March 19, 2002 as Application Serial No. 10/088,628
and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, § 1.56.

FOREIGN PRIORITY RIGHTS: I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Serial Number	Filing Date	Priority Claimed?

PROVISIONAL PRIORITY RIGHTS: I hereby claim priority benefits under Title 35, United States Code, § 119(e) and § 120 of any United States provisional patent application(s) listed below filed by an inventor or inventors on the same subject matter as the present application and having a filing date before that of the application(s) of which priority is claimed:

Serial Number	Filing Date	Status
60/156,860	September 30, 1999	Expired

NON-PROVISIONAL PRIORITY RIGHTS: I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

COMBINED DECLARATION AND POWER OF ATTORNEY

Serial Number	Filing Date	Status
PCT/US00/26634	September 28, 2000	Pending

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Paul T. Clark, Reg. No. 30,162, Karen L. Elbing, Ph.D. Reg. No. 35,238, Kristina Bieker-Brady, Ph.D. Reg. No. 39,109, Susan M. Michaud, Ph.D. Reg. No. 42,885, James D. DeCamp, Ph.D., Reg. No. 43,580, Sean J. Edman, Reg. No. 42,506, Timothy J. Douros, Reg. No. 41,716, Vicki Healy, Reg. No. 48,343.

Address all telephone calls to: Karen L. Elbing, Ph.D., at 617/428-0200.

Address all correspondence to: Karen L. Elbing, Ph.D. at Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110. **Customer No: 21559**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Full Name (First, Middle, Last)	Residence Address (City, State, Country)	Post Office Address (Street, City, State, Country)	Citizenship
Jerrold Rosenbaum	Newton, Massachusetts	587 Walnut Street Newton, MA 02460	United States
Signature: <i>Jerrold Rosenbaum</i> MA			Date: <i>4/7/02</i>

Commonwealth of Massachusetts
Suffolk.....S.S. Date *4/7/02*.....
 Then Personally appeared the above named
Jerrold Rosenbaum
 and acknowledged the foregoing instrument
 to be his/her free act and deed before me,
 Donald Novak, Notary Public
 My commission expires ~~7 September 2001~~
22 AUGUST 2005
Donald Novak